Overview of Long-Term Goal 2:
State-of-the-Science Risk Assessment Models, Methods, and Guidance

Background

The Human Health Risk Assessment (HHRA) Program's Long-Term Goal (LTG) 2 provides the critical models, methods, and guidance used to produce hazard and dose-response assessments done under LTG 1 as well as the exposure assessments integral to risk assessments that underlie human health regulatory decisions by most EPA programs. LTG 2 thus strengthens much of the Agency's mission by supporting as intermediate clients those in the NCEA or others within EPA or elsewhere doing hazard and dose-response assessments or using such hazard and dose-response assessments to produce complete risk assessments.

Additionally, National Center for Environmental Assessment (NCEA) has played a leadership role in developing exposure factors guidance for the Agency as noted by distinguished awards (e.g., the U.S. Environmental Protection Agency [EPA] gold medal for the Children's Age-Binning Exposure Guidance). The Exposure Factors handbook and children's exposure factors work are some of the most highly cited and used products in Agency program and site-specific decisions and serve as hallmark examples of the Human Health Risk Assessment (HHRA) Program's contribution to reducing the adverse health and ecological effects caused by pollution.

The purpose of this LTG description is to portray, in concert with poster presentations, the relevance of the LTG 2 program on models, methods, and guidance to EPA decision-making, leadership in risk assessment, scientific quality, and performance. Ongoing activities are used to illustrate these attributes. Linkages to the development of assessments under the Human Health Risk Assessment (HHRA) Program's LTG 1 and LTG 3 are highlighted.

Relevance

This NCEA program is designed to provide the best possible tools to those doing the chemical assessments described under LTG 1 and LTG3 of this Multi-Year Plan (MYP). The program uses its experience in the LTG 1 chemical hazard and dose-response assessments to identify critical issues in the evolving practice of risk assessment and to develop and test methodological approaches in the context of specific datasets. The experience includes the initial assessment of the scientific data and issues but is also informed by the subsequent dialogues and critiques from internal and external peer reviews, public comments, and other discussions of those assessments. In addition, the program follows general developments and debates about risk assessment, such as embodied in the Executive Order on assessing risk to children and other Executive Orders, statutes, and draft Bulletins regarding the quality of analyses and the need for risk assessments that appropriately inform decision-making. This work on methods and tools is needed to assure the Integrated Risk Information System (IRIS) assessments continue

to be the "gold standard" and that risk assessments continue to address the needs of decision-makers.

Some parts of the program, notably work on exposure factors, support for guidance development, and some of the work on susceptible populations, address the needs (other than the need for IRIS assessments) of risk assessors throughout EPA and the States. With respect to exposure factors work, we receive resounding support from Regional and Program offices (and internationally) that that database and program is a key resource for risk assessments of many kinds. To assure that we are addressing priority client needs, we have reached out to risk assessors to clarify what aspects of exposure factors merit further work and used that guidance to assure continuing relevance. The program has also provided key support and leadership based on input from both internal and external parties as to the priorities for guidance for efforts such as the *Cancer Guidelines* revision.

LTG 2 has been organized to address the path from environmental concentrations, to exposures, internal dose, biologically effective dose, and health impacts to facilitate an appropriate characterization of the risks for use in decision-making. Certain concepts or aspects of risk assessment methodology (e.g., concepts identifying and describing modes of action [MOAs]) and developments in the kinds of risk questions asked (e.g., questions characterizing susceptible populations or other population variability or uncertainty) cut across this structure. They are integral to capturing variability and uncertainty in risk assessment. Figure 1 illustrates the life cycle of effects from source emissions to health impact.

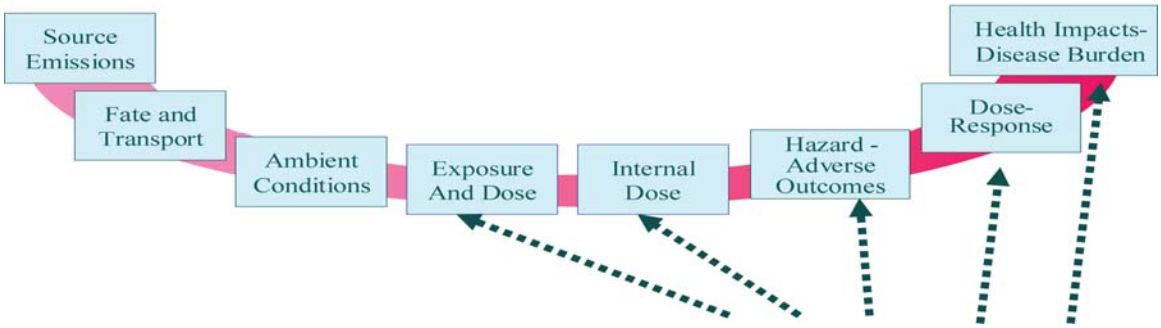

Figure 1. Reducing Uncertainty and Risk Characterization Source-to-Health Impact Continuum. The HHRA program improves risk characterization by developing methods, models, and databases and providing guidance to improve assessment of the critical links across the five-step exposure-to-effect portion of the paradigm.

- ***Approaches for Assessing Environmental Exposures***
- ***Internal Dose and Physiologically-Based Pharmacokinetic Modeling***
- ***Hazard Characterization***
- ***Dose-Response Analysis***
- ***Risk Characterization***

(1) Approaches for Assessing Environmental Exposures:

- Exposure work is done in support of the needs of multiple risk assessors across EPA and States, with particular focus on information for which there are multiple clients such that a common centralized database or approach is of the greatest value.

(2) Internal dose and Physiologically-based pharmacokinetic (PBPK) modeling:

- More complex chemical assessments frequently include evaluation of PBPK models. This includes evaluation of how differences in metabolism affect risk estimation, either in considering when data is available from only one route-of-exposure, to evaluate if PBPK explains differences across species, and for high-to-low-dose extrapolation.

(3) Hazard Characterization:

- Hazard characterization efforts include identifying likely human health effects to a chemical including consideration of susceptible populations (e.g., lifestage and genetic predisposition) and use of mode of action (MoA) in risk assessment. MOA efforts include applying available data to better inform decisions on the relevance of high dose effects to low level environmental exposures, within and between species, impact on susceptible populations (e.g., lifestage and genetic predisposition) and the quantitative impacts of these factors on dose-response functions used in risk assessment

(4) Dose-Response Analysis:

-Quantitatively relating exposure or dose to likely effect has received increased interest for nongenotoxic modes of action. There is a renewed need to consider appropriate dose-response models in the range of observed data and the underlying reasons for the default linear low-dose extrapolation for carcinogens and potential alternatives to that. The program has several projects in response to that need, including efforts specifically on low-dose extrapolation and the development of versions of existing dose-response models that can take into account potential additivity to background doses or background processes.

(5) Risk Characterization

-Quantitative analysis of uncertainty, derivation of central estimates and confidence limits on estimates of risk is another need driven in part by those who wish to use risk assessment results in the context of formal decision analysis or in cost-benefit analysis. These efforts also inform the relationship between adverse outcomes and the impact of environmentally-induced burden of disease on human health.

Additional evidence of the relevance of the LTG 2 methodological developments is provided in the LTG 2 poster discussions of specific areas in which methods are being developed. Further evidence appears in the LTG 1 and LTG3 poster presentations, which often highlight how individual assessments rely upon the methodological tools developed in the past and how the assessments serve as test beds for the ongoing development of methods and tools.

Quality and Leadership

The work under LTG 2 supports NCEA's assessment needs in LTG 1 and LTG 3 and informs assessment needs and decisions in EPA program offices and regions. Our goal is to develop methods, tools, and databases that are of outstanding quality judged against a range of quality measures:

- relevance to critical risk assessment issues;
- solid scientific basis for the work;
- clarity and transparency to both scientific reviewers and to those using a tool; and
- improved ease of use for tools such as the benchmark dose software (BMDS).

To pursue these avenues, NCEA has formed collaborative partnerships across the Agency and with outside partners and is involved in EPA workgroups, projects, and publications. For example, NCEA has organized and led efforts to obtain external consultations with the National Academy of Science on future of risk assessment and a series of workshops on specific issues as it relates uncertainty and variability analysis in risk assessment. As another example, work on databases of physiological parameters for PBPK modeling has been done in collaboration with ORD's National Center for Computational Toxicology (NCCT) and National Health and Environmental Effects Research Laboratory (NHEERL), and NCEA's work on uncertainty in PBPK modeling was done in collaboration with NCCT. We advise and work collaboratively with various international agencies (e.g., WHO, IARC), ATSDR and the State of California in developing approaches to address characterizing risk to susceptible populations and incorporating MOA information into state of the art risk assessments.

The accompanying posters provide a more detailed overview of the science questions stemming from the exposure-to-effect portion of the source-to-health impact paradigm along with the plans for addressing them. Individual posters describe and provide examples of methods, models, databases, and risk assessment guidance developed under this program.

Approaches for Assessing Environmental Exposures.

Poster 1, Approaches for Assessing Environmental Exposures, addresses exposure factors and methods development, with methods currently focused on dermal assessments. The exposure factors program is designed to answer questions such as, "What factors result in interindividual variability in exposure?" and "Are certain members of the population more highly exposed than the general population?" Dermal exposure is a critical area of exposure uncertainty for EPA's Office of Solid Waste and Emergency Response (OSWER). The exposure factors database continues to provide updated information on risk assessment inputs common to many assessments, with recent work focused on needs identified by our clients for guidance on assessing tribal fish consumption. Additional support has been devoted to characterizing distributions of risks and to summarizing distributions of variability of exposure factors and how such inputs differ across age groups.

Human epidemiological studies provide important support for hazard judgments and in some cases for quantitative dose-response estimation. One frequent limitation results from uncertainty about exposures. LTG 2 projects are addressing measurement error correction, exposure misclassification, and approaches for better characterizing uncertainties in epidemiological studies. Another challenge in developing inferences from epidemiological studies is the low statistical power of many individual studies, particularly for relatively rare outcomes. With respect to evaluating human epidemiological data, the HHRA program is exploring the use of meta-analysis and similar techniques in the complex assessments of criteria pollutants in LTG 3 and in more recently in LTG 1 for trichloroethylene assessment.

Internal Dose and Physiologically Based Pharmacokinetic Modeling.

Innovations in approaches for dosimetric adjustment for inhalation exposures are described in **Poster 2, Chronic RfC and Exposure-Response Methodologies in Revision and Under Development.** The program is working to revise and update the chronic RfC methodology, released in 1994. Developments include updates to dosimetry adjustment methods and consideration of adjustments for less than lifetime exposure scenarios. The RfC methodology and other ongoing revisions are relevant to Office of Air and Radiation (OAR), OSWER, and Regional needs in developing values for inhalation dosimetry. These efforts on dosimetry also parallel and complement efforts under LTG3 on dosimetry for criteria pollutants (poster 4).

Poster 3, Advancing the Development, Evaluation, and Use of Physiologically-based Pharmacokinetic (PBPK) Models in Risk Assessment, describes how PBPK models are increasingly being used in the derivation of points of departure (PODs) when data are only available on one route of exposure. An important component of these models are physiological parameters such as organ size and blood flows and biochemical parameters such as information about common phase I and II metabolic enzymes. NCEA is developing a comprehensive literature review database on physiological and enzyme parameters for PBPK modeling, including how those differ by lifestages. This will allow PBPK modelers to utilize common data and also allow PBPK modeling to be useful for assessing early-life risks and exploring population variability due to PBPK variation. All of these efforts have immediate utility in the more complex or high-impact assessments where the complexity of PBPK model considerations is needed. These efforts on PPBK modeling have relevance to chemical assessments under LTG1 (See posters 8, 10).

Hazard Characterization.

Approaches for identifying and characterizing hazards to susceptible populations are described in **Poster 4, Utilizing Early Lifestage Data in Risk Assessment**, and **Poster 5, Characterization of Environmental Risks of Older Adults.** Susceptibility is defined here as a difference in potential for adverse health effects resulting from differential exposure or intrinsic biological factors (e.g., lifestage and genetic predisposition). The effort addresses characterization of differences between children (**Poster 4**), the aged (**Poster 5**), and adults that can lead to disparity in adverse outcomes following environmental exposure. Some efforts, such as the *Child-Specific Exposure Factors Handbook* will directly improve risk assessments by providing better estimates of

differential exposure (variations in dose) reflecting the behavior of children. Efforts include development of models and tools to assist IRIS chemical managers as they discuss childhood susceptibility. In the near term, other efforts such as reviewing information on the aging may do more to identify specific areas where research is needed. These efforts to identify and characterize health hazards have had an impact and will continue informs efforts under LTG1 (see poster 7) and LTG3 (see posters 8, 10).

Poster 6, Use of Mode of Action Data to Inform Human Health Risk Assessment, addresses how to use MOA data to inform decisions on critical issues such as the relevance of animal data for human health risk estimation and the quantitative impacts of the use of MOA information on dose-response analysis. MOA analyses often arise in evaluating the significance of animal data in our chemical assessments, and there is a clear need for better tools for evaluating hypotheses regarding MOAs (See LTG1 posters 4, 5, 6, 7 and LTG3 poster 7, 8). The program has reviewed a range of available frameworks for evaluating MOA information and is developing methods for situations where multiple MOAs may be operating, incorporating hypothesis testing approaches. MOA analysis also has had a significant contribution in the development of approaches for cumulative risk assessment.

Dose-Response Analysis.

Poster 7, Use of Biologically-Based Dose Response Models, details key potential uses of biologically based models in low-dose human risk extrapolation and for generating testable hypotheses to better understand MOAs. Several examples of "biologically motivated models" mathematically describe key attributes of the biology without modeling the full mechanism. One contribution of our program is exploring the sensitivity of such models to model assumptions and key parameters, in some cases parameters that are not directly measurable. Uncertainty and sensitivity analyses of biologically based dose response (BBDR) models inform risk assessment and can identify critical data gaps in our understanding of MOAs. Recently, our approach has been demonstrated as part of our formaldehyde health assessment where we found that certain model assumptions and minor changes in key parameters resulted in major quantitative uncertainty in modeling results.

EPA BMD software and guidance has been available since 2000 and is used by IRIS staff and by risk assessors nationally and internationally as a central feature of chemical dose-response assessments. This essential suite of analytical packages is currently being expanded with additional interface and reporting features and new modules that will enhance users' ability to analyze complex response measures such as continuous, time-dependent, and saturable endpoints. As described in **Poster 8, Development of Novel Approaches for Dose-Response Modeling,** we have developed a Markov-Chain Monte Carlo method to estimate a distribution of risk estimates around a specific dose (for a specified dose-response curve) that can facilitate estimation of expected value central estimates as well as upper-and lower-bound estimates. Improvements in BMD approaches also affect cancer dose-response modeling, providing a statistically valid approach for constructing expected value central estimates and for generating confidence intervals for the multistage model, time-dependent modeling, lognormal distributions,

and development of approaches for model averaging. These efforts are motivated by user-identified needs in the BMD tools available to chemical risk assessors. The relevance of these methods is clearly demonstrated with specific application to unique chemical datasets in LTG1 (See poster 9) Experience with diverse datasets has raised special issues and motivated improvements to other models such as time-to-tumor modeling and categorical regression (CatReg) techniques.

One of the critical challenges in dose-response analysis is the evaluation of complex datasets and how to use all the data available from multiple endpoints, multiple species, and multiple durations of exposure. CatReg is an approach to quantitatively integrate information using regression analyses of study severity scores and exposure parameters including different durations. The categorization of observed responses allows expression of dichotomous, continuous, and descriptive data in terms of effect severity and supports the analysis of the data from single studies or a combination of similar studies (e.g., meta-analysis). The CatReg program is being applied in the analysis of health effects studies in numerous IRIS assessments. This approach adds to our armamentarium of dose-response tools that move us away from single point risk estimates and facilitates use of risk estimates in benefits analysis (e.g., compound T case study).

The application of cumulative risk assessment principles to health assessments is illustrated in **Poster 9, Whole Mixture Methods for Assessing Health Risks from Exposures to Chemical Mixtures.** Cumulative risk assessment is a real-world problem and highly relevant to evaluating food-use pesticides, Superfund sites, and many regional assessments. EPA's Office of Prevention, Pesticides, and Toxic Substances (OPPTS), OSWER, and the Regions are principal clients of the approaches developed under this program. The health risk assessment of complex mixtures is challenging because of variations in chemical composition that can change the relationship between mixture dose and response. Strategies have been developed to test whole mixtures and then extrapolate the resulting toxicity information to assess health risks from environmental exposures to similar mixtures. Whole mixture risk assessment methods include (1) direct toxicological or epidemiological evaluation of the environmental mixture (or a concentrate) (2) use of surrogate information on a sufficiently similar mixture, and (3) evaluation of mixture fractions.

Poster 10, Component-Based Methods for Assessing Health Risks from Exposures to Chemical Mixtures, describes how component based methods can be utilized in a number of specific risk assessment efforts:

- Draft Relative Potency Factors (RPFs) for polycyclic aromatic hydrocarbons (PAHs) [see LTG 1, Poster 12] and analyses of RPF uncertainties for pesticides;
- Improved design of mixtures toxicity experiments;
- Use of MOA data for disinfection byproducts (DBPs) and organotins (OTs);
- Exposure assessments for dioxins, polybrominated flame retardants (PBDEs), DBP's, and OTs; and
- Approaches to integrate mixtures exposure and risk assessment methods with emerging cumulative health risk assessment issues.

These different approaches have different strengths and weaknesses, including assumptions and attendant uncertainties. The utility of these different approaches is based upon the available data. Some programs, such as OPPTS and OSWER, require tools for evaluating the cumulative health risk impact of multiple chemicals, and HHRA program continues to develop tools and applications of those. These methods also have direct relevance to efforts under LTG3 (See poster 9).

Health Impacts–Disease Burden.

Quantitative analysis of uncertainty, derivation of central estimates and confidence limits on estimates of risk is another need driven in part by those who wish to use risk assessment results in the context of formal decision analysis or in cost-benefit analysis. These efforts also inform the relationship between adverse outcomes and the impact of environmentally induced burden of disease on human health. The importance of characterizing uncertainty is directly relevant to assessments in LTG1 and LTG3.

Poster 11, Evaluation of Uncertainty, Data Derived Uncertainty Factors, Variability, shows how, as part of melding the general with the specific, NCEA is examining what can said about uncertainty factors used in the current reference value paradigm and how those could be modified to reflect increasing knowledge or chemical-specific information. As NCEA evaluates these issues, it also is working to increase the amount of information on uncertainty, on sensitivity to assumptions or choices made in a risk assessment, and to variability in population sensitivity in individual chemical assessments and how it is communicated to users. A number of the assessments being completed for external review in FY07 are providing case examples for presentation of uncertainty information in assessments. This effort has significant importance to our chemical assessment program in LTG1 (See poster 10) and LTG3 (see Poster 7 for implications on noncancer effects of ozone).

Poster 12, Approaches to Address New and Emerging Issues in Risk Assessment, illustrates how, in addition improving risk assessment practices in areas of traditional experience, NCEA scientists are also involved in assessing emerging issues in risk assessment and developing and adapting approaches, methods, and guidance for using new kinds of information. Some of the projects NCEA is involved in that will address these emerging issues include:

- Nanotechnology Risks
- Use of Genomics Data
- Risk Assessment for Microbes
- Computational Approaches Addressing Limited Toxicity Information

Poster 13, Promotion and Collaboration to Enhance Use and Development of State-of-the-Science Risk Assessment Models, Methods, Databases and Guidance, describes how such promotion and collaboration allows for timely incorporation of recent scientific advances into risk assessment practice. These efforts also provide improved tools for application in the decision-making needs of the EPA programs and regions, and serves as a model for other government entities, from the local to international levels. HHRA program provides a leadership role in the development of EPA's risk assessment

guidelines, guidance documents, and technical reports that are premier sources of guidance to inform the decision-making process for risk assessors and risk managers from EPA Program Offices, EPA Regions, States, and Local Regulatory Authorities. Formerly, the Risk Assessment Forum (RAF) was established within NCEA to promote consensus on risk assessment issues. Recently, the RAF was moved into the office of the science advisor and is no longer part of HHRA. However, NCEA scientists do continue to serve on Technical Panels of the RAF. NCEA has led crosscutting groups of Agency scientists to address Agency risk assessment issues through the RAF and the science policy council.

Program Performance

NCEA is recognized within and outside the Agency as a leader in environmental risk assessment. NCEA staff chair three of the eight standing committees of the EPA's Risk Assessment Forum. NCEA is a visible presence at relevant professional societies both presenting and organizing relevant sessions and actively contributing to discussions. Products such as the BMDS have become standard tools for assessors outside as well as within the EPA.

Table 1. Key Accomplishments in LTG 2 during 2005-2007

- **Publication of:**
  - **Final revised *Cancer Guidelines* and *Children's Supplemental***
  - ***Approaches for the Application of Physiologically-Based Pharmacokinetic (PBPK) Models and Supporting Data in Risk Assessment***
  - ***Summary of the NCEA Colloquium on Current Use and Future Needs of Genomics in Ecological and Human Health Risk Assessment* (Final Report)**
  - ***Use of Physiologically Based Pharmacokinetic (PBPK) Models to Quantify the Impact of Human Age and Interindividual Differences in Physiology and Biochemistry Pertinent to Risk* (Final Report) and the *All-Ages Lead Model* (AALM) Version 1.05 (External Review Draft)**
  - ***A Framework for Assessing Health Risk of Environmental Exposures to Children* (Final Report)**
  - ***Child-Specific Exposure Factors Handbook 2006* (External Review Draft)**
  - ***Age Binning Exposure Guidance* (Final Report)**
  - ***Aging and Toxic Response: Issues Relevant to Risk Assessment* (Final Report)**
- **Updates of BMD model for analysis of endpoints with continuous data**
- **Development of CatReg models for analysis of endpoints across multiple domains for toxicity (e.g., functional observational data for neurological function)**

New approaches to risk assessment have been developed to address specific issues including new guidance for risk assessors, new approaches for evaluation of special populations, and new quantitative models. Table 1 shows key LTG 2 accomplishments completed during 2005 through 2007.

The cancer guidelines, while a RAF product with many contributors, were developed while the forum was still part of HHRA. These guidelines have had a broad impact on assessments affecting EPA programs and other Federal partners' risk assessment efforts (e.g., DOD). The PBPK model guidance has had important impacts on users of these models both within and outside the Agency. BMDS and CatReg are two highly used products in both the assessments done under HHRA and those of the Agency programs and others users outside the Agency.

The All-Ages Lead Model has been used by OPPTS in proposed rule making for lead abatement. The work on lifestage-related vulnerability to environmental exposures has had a significant impact on how the Agency deals with children's risk and serves as a touchstone for risk assessment guidance internationally.

Table 2 lists key areas (methods, models, guidance output) in which improvements are expected in the years 2008 through 2012. These methods, models, and guidance will improve extrapolation methods from animals to humans, across life stages, from higher-dose observations to lower doses, and for route-to-route extrapolation in cases where limited exposure data exists for a given route.

Table 2.Areas of Expected Output 2008-2012

- **Uncertainty analysis**
- **Application of MOAs information in risk assessments**
- **Physiologically-based pharmacokinetics (PBPK) modeling**
- **Approaches to quantification (e.g., BBDR, CatReg, meta-analysis approaches)**
- **Approaches for assessing risk of environmental exposures to age-susceptible populations in children, and the elderly**
- **Development of data arrays**
- **Less-than-lifetime durations**

Other efforts will improve qualitative and quantitative evaluation of variability and uncertainty in hazard characterization and dose-response analysis.

Conclusions

HHRA program provides leadership in the context of the more complex assessments of specific chemicals (see LTG 1 posters) with synergy between methods work and application. The expertise of our staff in their fields—exposure, dosimetry, epidemiology, cancer biology, developmental biology, clinical medicine, toxicology, and public health—are instrumental in achieving results and integrating emerging science into risk assessments methods, models and guidance. HHRA program is bringing cutting-edge science into the practice of risk assessment. It is working on ways to assess and consider situations in which chemicals might have multiple or uncertain MOAs. It is reexamining whether there have been advances in how low-dose extrapolation should be done (cf. report: State of the Science on Low-Dose Extrapolation – Issues and Practice). It is leading the way on gathering data on polymorphic enzymes for future use in risk assessments, application of PBPK modeling to chemical risk assessment and appropriately presenting information on variability and uncertainty. NCEA's role as primary practitioners of chemical risk assessment helps provide the strong link and understanding of the needs of other current practitioners wrestling with evolving scientific knowledge and its application to risk assessment science.